REDUCTIVE COUPLING OF (R)-(+)-CARVONE AND (+)-CAMPHOR BY THE TICI₄-Mg REAGENT. X-RAY CRYSTAL STRUCTURE OF (+)-(1<u>S</u>, 5<u>R</u>, 1'<u>S</u>, 5'<u>R</u>)-CARVONE PINACOL **

Marcel Pierrot^a, Jean-Marc Pons^b and Maurice Santelli^{*b}

(a) UA au CNRS nº 126; (b) UA au CNRS nº 109, Centre de St-Jérôme, Av. Esc. Normandie-Niemen, 13397 Marseille Cedex 13, Fr.

<u>Summary</u>: The reductive coupling of (R)-(+)-carvone by TiCl₄-Mg-<u>t</u>BuOH leads to (+)-(1<u>5</u>, 5<u>R</u>, 1'<u>5</u>, 5'<u>R</u>)carvone pinacol <u>3</u> (70 %). In presence of pentane, (-)-(1<u>R</u>, 5<u>R</u>, 1'<u>R</u>, 5'<u>R</u>)-carvone pinacol <u>4</u> (50 %) and ketol <u>5</u> (15 %) are isolated. Isoborneol (58 %) and borneol (32 %) result of the reduction of (+)-camphor with the same reagent.

The reductive coupling of ketones is known to give pinacols.^{1,2} From classical methods (alkali metals, ³ Al(Hg), ⁴ MeMgBr-FeCl₃, ⁵ Mg, ^{3a,6} electrochemical means ⁷), the reaction is considered as irreversible, giving mainly kinetic products. With α , β -enones, the reductive dimerisation is complicated by the likely presence of products resulting from β -coupling (diketone hydrodimers) and cross-coupling (γ -ketols).^{7a,b,f} It should be pointed out that few works have been devoted to the stereochemistry of products. ^{3d,4b}

From the seventies onwards, considerable attention has been given to the reductive coupling of ketones by the low valent titanium species.^{4b,8} We present our results concerning the reductive coupling of two hindered ketones, (\mathbb{R})-(-)-carvone <u>1</u> and (+)-camphor <u>2</u>.

(-)-Carvone can be nicely reduced by the TiCl₄-Mg reagent (2 equiv.) in THF in the presence of <u>t</u>-BuOH (2 equiv.) leading to the major diol <u>3</u> (m.p. 172 °C)(70 % yield).⁹ The presence of only 10 signals in ¹³C NMR spectrum indicated a C₂-axis of symmetry, that is a <u>threo</u>-isomer. To differentiate the two <u>threo</u> isomers, <u>3</u> was subjected to single-crystal X-ray analysis which revealed it to be the (<u>15</u>, 5<u>R</u>, 1'<u>5</u>, 5'<u>R</u>)-isomer. ¹⁰ The other <u>threo</u> isomer (-)-(<u>1R</u>, 5<u>R</u>, 1'<u>R</u>, 5'<u>R</u>)(m.p. 78-79 °C), <u>4</u>, was sometimes isolated in minute quantity. We noted that the addition of pentane (or mesitylene) to the reaction mixture increased the amount of <u>4</u> (50 %) giving also a third compound, the ketol <u>5</u> (10 %) and <u>3</u> (15 %). The <u>erythro</u>-isomer, <u>6</u>, (20 signals expected in ¹³C NMR) was not detected.¹¹



**(+)-(1<u>S</u>, 5<u>R</u>, 1<u>'S</u>, 5<u>'R</u>)-1-(1'-Hydroxy-5'-isopropenyl-2'-methyl-2'-cyclohexenyl)-5-isopropenyl-2-methyl-2-cyclohexenol.







ORTEP Stereodrawings of Carvone-Pinacol_3 (m.p. 172 °C).

The mechanism of the reductive coupling of ketones by low valent titanium species is open to discussion. Results have been readily rationalized by metal bound ketyls,^{8a} or more recently, by a concerted electron transfer from the metal to the carbonyl group.¹²

The transition state is supposed to require a ground state conformation and an axial attack on each ketone.¹³ The coupling by overlap of the π -molecular orbitals (<u>Re</u> face for the first and <u>Si</u> face from the second molecule) can be ruled out by the absence of unsymmetrical <u>erythro</u> isomer <u>6</u>.



The major diol <u>3</u> results from the addition of the <u>Re</u> faces. In the transition state, each cyclohexenyl cycle presents an enhanced interaction with the isopropenyl group borne by the other cycle. In contrast, the ground state conformation of <u>3</u> with diaxal hydroxyl groups shows moderate non bonded interactions. ^{14,15}



The ground state conformation of the minor pinacol <u>4</u> coming from the addition by the <u>Si</u> faces with weak interactions, presents in each cyclohexenyl cycle a 1,3-trans relation between the isopropenyl group and the other cyclohexenyl cycle giving two severe interactions.



We assume that <u>3</u> results from a thermodynamic control and <u>4</u> from a kinetic control, since the experimental conditions have not excluded the reversibility of the pinacol condensation.¹⁶ The problem of the thermodynamic isomerization during the pinacol coupling has been already discussed ^{4b} from the McMurry's observations (for tertiary pinacols no retropinacol condensations occurred with Ti(0) species ¹⁷).

In conclusion, we suggest that with the TiCl₄-Mg reagent, the distribution of the products can evolve toward the formation of the thermodynamic product. The reversibility of the reaction could be slow down by addition in the reaction mixture of hydrocarbon.

The action of the TiCl₄-Mg reagent (2 equiv.) in presence of <u>t</u>-BuOH (2 equiv.) on (+)camphor does not give the dimeric products but only the secondary alcohols isoborneol <u>7</u> (58 %) and borneol <u>8</u> (32 %).¹⁸ In this case and contrary to the dissolving alcali metal reduction 3b,c,e,f,g , the overcrowding around the carbonyl group prevents the reductive duplication.



References and Notes

1 - House, H. O. "Modern Synthetic Reactions", W.A. Benjamin, 2^{sd} Edition, 1972, p. 156, 166, 183.

2 - Thomas, H.G. "Methoden der Organischen Chemie" (Houben-Weyl), 4th Edn, 1976, E. Muller Ed., Vol. 7/2b, G. Thieme Verlag, p. 1870.

3 - (a) Majerus, G.; Yax, E.; Ourisson, G. <u>Bull. Soc. Chim. Fr.</u> 1967, 4143. (b) Coulombeau, A.; Rassat, A. <u>J. Chem. Soc. Chem. Comm.</u> 1968, 1587. (c) Huffman, J.W.; Charles, J.T. <u>J. Am. Chem. Soc.</u>, 1968, <u>90</u>, 6486. (d) House, H.O.; McDaniel, W.C.; Sieloff, R.F.; Vanderveer, D. <u>J. Org. Chem.</u> 1978, <u>43</u>, 4316. (e) Rautenstrauch, V. <u>Helv. Chim. Acta</u> 1982, <u>65</u>, 402. (f) Pradhan, S.K.; Thakker, K.R.; McPhail, A.T. <u>Tetrahedron Lett.</u> 1987, <u>28</u>, 1813. (g) Huffman, J.W.; Wallace, R.H.; Pennington, W.T. <u>ibid</u>. 1988, <u>29</u>, 2527.

4 - (a) Munoz-Madrid, F.; Pascual, J. <u>Anales de Quim.</u> 1978, <u>74</u>, 1270. (b) Mundy, B.P.; Srinivasa, R.; Kim, Y.; Dolph, T; Warnet, R.J. <u>J. Org. Chem.</u> 1982, <u>47</u>, 1657.

5 - Meinwald, J.; Hendry, L. ibid. 1971, 36, 1446.

6 - Dunogues, J.; Calas, R.; Bolourtchian, M.; Biran, C.; Duffaut, N. <u>J. Organomet. Chem.</u> 1973, <u>57</u>, 55 and ref. therein.

7 - (a) Bladon, P.; Cornforth, J.W.; Jaeger, R.H. <u>J. Chem. Soc.</u> 1958, 803. (b) Bowers, K.W.; Giese, R.W.; Grimshaw, J.; House, H.O.; Kolodny, N.H.; Kronberger, K.; Roe, D.K. <u>J. Am. Chem. Soc.</u> 1970, <u>92</u>, 2783. (c) Grimshaw J.; Trocha-Grimshaw, J. <u>J. Chem. Soc. Perkin</u> | 1973, 2584. (d) Touboul, E.; Dana,

G. <u>Tetrahedron</u> 1975, <u>31</u>, 1925. (e) Margaretha, P.; Tissot, P. <u>Nouv. J. Chim.</u> 1979, <u>3</u>, 13. (f) Mandell, L.; Hamilton, H.; Day Jr, R.A. <u>J. Org. Chem.</u> 1980, <u>45</u>, 1710. (g) Tissot, P.; Surbeck, J.P.; Gulacar, F.O.; Margaretha, P. <u>Helv. Chim. Acta</u> 1981, <u>64</u>, 1570. (h) Baizer, M.M. <u>Tetrahedron</u> 1984, <u>40</u>, 935. (i) Orliac-Le Moing, A.; Delaunay, J.; Lebouc, A.; Simonet, J. <u>ibid.</u> 1985, <u>41</u>, 4483. (j) Fournier, F.; Davoust, D.; Basselier, J.J. <u>ibid.</u> 1985, <u>41</u>, 5677.

8 - (a) McMurry, J.E. <u>Acc. Chem. Res.</u> 1983, <u>16</u>, 405. (b) Pons, J.M.; Santelli, M. <u>Tetrahedron</u> 1988, <u>44</u>, 4295. (c) Kahn, B.E.; Rieke, R.D. <u>Chem. Rev.</u> 1988, <u>88</u>, 733.

9 - For experimental procedures, see (a) Pons, J.M.; Santelli, M. <u>Tetrahedron Lett.</u> 1986, <u>27</u>, 4153 and ref. 12b.

10 - This material of composition $C_{20}H_{30}O_2$ crystallized (THF, 5 °C) in orthorombic system, space group $P2_12_12_1$ with a = 7.818 (2) Å, b = 9.920 (3) Å, c = 23.476 (7) Å. The intensities are collected on a CAD4 Enraf-Nonius diffractometer (MoK $_{\alpha}$, λ = 0.7107 Å). The structure was solved by direct methods (Multan), current R = 0.043 for 1298 independant reflections with I>3 σ (I). Details on the structure can be obtained on request.

11 - Electrochemical reduction of (+)-carvone is known to give two E-diketone hydrodimers, see ref. 7c.

12 - (a) J.M. Pons, Thesis, Marseille, 1987. (b) Pons, J.M.; Santelli, M. J. Org. Chem. 1988, 53, 000.

13 - (a) Trost, B.M.; Florez, J.; Jebaratnam, D.J. <u>J. Am. Chem. Soc.</u> 1987, <u>109</u>, 613. (b) Wu, Y.D.; Houk, K.N.; Trost, B.M., <u>ibid.</u> 1987, <u>109</u>, 5560. (c) El Idrissi, M.; Santelli, M. <u>J. Org. Chem.</u> 1988, <u>53</u>, 1010.

14 - Nethertheless, the central $C^{1}-C^{7}$ bond length was found by X-ray analysis to be 1.596 (4) Å. This bond elongation shown a steric repulsion among the bulky substituents and a weakness of this CC bond, for a discussion, see : Osawa, E. "Molecular Structure and Energetics", VCH Publishers, Vol. 3, 1986, p. 329.

15 - It should be emphasized that any tetrahedral angles around the functionnalized carbon atoms present no very significant alterations. This is in contradiction to the statement that predicted the presence of large values due to distortions caused by bulky substituents ("Thorpe-Ingold effect"), see : Kuhn, L.P.; Von R. Schleyer, P.; Battinger Jr., W.F.; Eberson, L. J. Am. Chem. Soc. **1964**, <u>86</u>, 650. Bond angle values in degrees : 01,C1,C2 : 109.5 (3); 01,C1,C6 : 109.0(2); 01,C1,C7 : 105.1(2); C2,C1,C6 : 112.3(3); C2,C1,C7 : 108.1(2); C6,C1,C7 : 112.6(3); C1,C7,O2 : 108.2(2); C1,C7,C8 : 109.4(3); C1,C7,C12 : 113.0(3); O2,C7,C8 : 106.5(2); O2,C7,C12 : 107.2(3); C8,C7,C12 : 112.2(3).

16 - In basic medium, hindered bis-allyl-pinacols are subject to a fragmentation reaction giving rise to one molecule of the corresponding enone and one molecule of the saturated ketone; see ref. 3a.

17 - McMurry, J.E.; Choy, W. J. Org. Chem. 1978, 43, 1800.

18 - The reaction rate is particularly slow (about 3 days at room temperature).

(Received in France 20 July 1988)